**IN THE UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF TEXAS**
**HOUSTON DIVISION**

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|---|---|---|
| **THOMAS WHITAKER, AND** | § | |
| **PERRY WILLIAMS,** | § | |
| **Plaintiffs,** | § | |
| | § | |
| **v.** | § | **CIVIL ACTION NO: 4:13-CV-2901** |
| | § | |
| **BRAD LIVINGSTON,** | § | |
| **EXECUTIVE DIRECTOR, TEXAS** | § | |
| **DEPARTMENT OF CRIMINAL** | § | |
| **JUSTICE, WILLIAM STEPHENS,** | § | |
| **DIRECTOR, CORRECTIONAL** | § | |
| **INSTITUTIONS DIVISION,** | § | |
| **TEXAS DEPARTMENT OF** | § | |
| **CRIMINAL JUSTICE, JAMES** | § | |
| **JONES, SENIOR WARDEN,** | § | |
| **HUNTSVILLE UNIT,** | § | |
| **HUNTSVILLE, TEXAS AND** | § | |
| **UNKNOWN EXECUTIONERS,** | § | |
| | § | |
| **Defendants.** | § | |

**PLAINTIFFS' RESPONSE TO COURT'S APRIL 1, 2015 ORDER**

TO THE HONORABLE UNITED STATES DISTRICT JUDGE:

Pursuant to this Court's order of April 1, 2015 [Doc. 58], Plaintiffs' file this response and include as Exhibit A, the Expert Report of James H. Ruble.

Respectfully submitted,

*/s/ Bobbie L. Stratton*
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**CERTIFICATE OF SERVICE**

I hereby certify that on this 24th day of April, 2015, the foregoing pleading was filed using the electronic case filing system of this Court. Thus, counsel of record for Defendants, who have consented to accept this Notice as service by electronic means, was served via the electronic filing system.

*/s/ Bobbie L. Stratton*
Bobbie L. Stratton

**James H. Ruble, R.Ph., Pharm.D., J.D.**
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April 24, 2015

Bobbie L. Stratton
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Re: Case No. 4:13-cv-02901; *Whitaker, et al. v. Brad Livingston, et al.*; In the United States District Court for the Southern District of Texas, Houston Division

Dear Ms. Stratton:

My name is James H. Ruble. On behalf of Plaintiffs Thomas Whitaker and Perry Williams in the above-referenced case, you have asked me to provide information responsive to the April 1, 2015 Order of the District Court of the Southern District of Texas that plaintiffs "file a precise scientific description of the process of compounding pentobarbital." The opinions I express in this report are made to a reasonable degree of scientific certainty.

I reside in Bountiful, Utah, located in the metropolitan area of Salt Lake City. I have been a registered pharmacist in the State of Utah since 1992. I earned a Doctor of Pharmacy, a Juris Doctor, a Bachelor of Science in Pharmacy, and a Bachelor of Science in Biology from the University of Utah, in Salt Lake City. I am a pharmacist at the University of Utah Health Care System, and I am an associate professor (clinical) in the Department of Pharmacotherapy and an adjunct assistant professor in the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah College of Pharmacy. I teach pharmacy law, health care ethics, and pharmaceutical compounding to professional pharmacy students and graduate students. My curriculum vitae, detailing prior positions, Honors, Research and Scholarly Work, Publications, and Presentations, is attached as Exhibit A.

In preparation of this report, I was provided and reviewed a copy of the April 1, 2015 Order. I also reviewed the U.S. Food and Drug Administration ("FDA") Guidance on Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA"),[1] FDA Guidance on Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal FDCA,[2] and the guidelines provided in:

[1] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052

[2] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377051

1. United States Pharmacopeia ("USP") General Chapter <797> Pharmaceutical Compounding – Sterile Preparations ("USP <797>");
2. USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations ("USP <795>");
3. USP General Chapter <85> Bacterial Endotoxins Test ("USP <85>");
4. USP General Chapter <71> Sterility Tests ("USP <71>"); and
5. USP Monograph for Pentobarbital Sodium Injection.

These USP sections are from version USP 37/NF 32 and are designated as "official" through 30 April 2015.

## A. PHARMACEUTICAL COMPOUNDING

The 2013 Drug Quality and Security Act (Public Law 113-54 – Nov. 27, 2013)[3] established two types of pharmaceutical compounding: traditional and non-traditional. These two activities are frequently referred to as "503 A" compounding and "503 B" compounding, respectively. Traditional (503 A) compounding does not involve the creation of drugs from scratch. Rather, it uses active and inactive ingredients to meet the individual needs of a specific, identifiable patient that for medical reasons cannot be met with an FDA-approved product, according to a legal prescription for an individual patient.

Non-Traditional (503 B) compounding also involves the use of active and inactive pharmaceutical ingredients to compound pharmaceutical preparations. However, the final preparation is not intended for a specific, identifiable patient; thus is not "patient specific" but is intended for general sales and distribution. Non-traditional compounding is commonly referred to as "outsourced" compounding and resembles drug manufacturing more than it does the professional practice of pharmacy. Unlike manufacturers, compounding pharmacies are generally not subject to the drug approval process and the rigorous checks and regulatory procedures required under current Good Manufacturing Practice For Finished Pharmaceuticals ("cGMPs").[4] Non-traditional compounders must nonetheless register with the FDA and acknowledge the jurisdiction and authority of the FDA to inspect their facilities. Whether a drug is compounded by a Traditional or Non-traditional compounder, the FDA does not verify the safety or effectiveness of these drug preparations or the quality of their manufacture. These compounded products thus remain outside the FDA regulatory framework that otherwise ensures these qualities in manufactured pharmaceutical drugs.

The intended use of a compounded drug customarily dictates the formula to be used, compounding method(s), appropriate storage conditions, and calculation of an appropriate "beyond use date" ("BUD"). The intended uses of drugs are frequently supported by one or more

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[3] Available at http://www.gpo.gov/fdsys/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf

[4] 21 CFR Part 211. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

published descriptions in a life science, clinical science, or pharmaceutical science database. This publication process is fundamental to the concept of "evidence based medicine" ("EBM")[5] and Good Clinical Practice[6] philosophies. For purposes of the writing of this report, I conducted searches in the National Library of Medicine (PubMED) database and the International Pharmaceutical Abstracts ("IPA") database, using the terms "pentobarbital" and "execution." According to these databases, there is no published scientific description of, or formula for, the process of compounding pentobarbital for use in executions. As such, it is highly probable there is no scientific, evidence-based formula existing in the public domain for this use.

There are, however, USP guidelines that govern the methods by which compounding pharmacies should prepare pharmaceutical preparations for medicinal use via intravenous ("IV") route of administration. I describe below these general guidelines and how they might be used to guide a pharmacy in compounding pentobarbital sodium injection.

## B. THE PROCESS FOR COMPOUNDING PENTOBARBITAL FOR MEDICINAL USE VIA INTRAVENOUS INJECTIONS

Pentobarbital is a short-acting barbiturate licensed by the FDA for human use as a sedative, hypnotic, pre-anesthetic, and anticonvulsant, in the emergency control of certain acute convulsive episodes.[7] In most of the clinical indications of pentobarbital sodium injection, it is administered either as an Intramuscular ("IM") injection into a large muscle or as a direct injection into an IV catheter.

In circumstances in which commercial pentobarbital sodium injection is unavailable for use, either due to shortage or other supply chain disruption, some pharmacies may have the equipment and expertise to prepare a compounded "copy" of the commercial product. This would entail use of the bulk active pharmaceutical ingredient ("API") and inactive ingredients. An API is any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation. Pentobarbital sodium salt is the bulk powder form needed to make finished compounded preparations of pentobarbital. Without pentobarbital sodium salt API, it is not possible to compound pentobarbital sodium injection. Quality API is pivotal to a quality final product.[8]

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[5] *See e.g.*, Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992;268(17):2420-2425.

[6] Good Clinical Practice ("GCP") is developed by the International Conference on Harmonization ("ICH") of Technologies. The FDA has guidance about use of GCP in U.S. Health Care, available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

[7] Pentobarbital sodium injection, product labeling. Available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5c380ab0-4386-48b6-80ab-ca594b23bc74

[8] I recently reviewed the current availability of pentobarbital sodium salt API in the United States by consulting primary commercial sources upon which U.S. compounding pharmacies rely for purchase of bulk chemical APIs. From my review, I concluded that pentobarbital API in bulk powder form is not currently available for sale for purchase by compounding pharmacies in the U.S. for use in compounded pentobarbital preparations.

The compounding of pentobarbital for IV administration must be conducted as "sterile" compounding because the preparation is administered directly into the systemic circulation of the body and bypasses mechanisms which protect humans from microbial infection and other potentially harmful toxins including, but not limited to, endotoxins and pyrogens. USP <797> (attached to this Report as Exhibit B), established in 2004, provides professional standards and guidance in pharmaceutical compounding of sterile preparations. Preparations compounded in conformance with USP <797> are referred to as "compounded sterile products" ("CSP"s). USP <797> establishes three levels of sterile compounding, based on risk of contamination, to wit: low-risk; medium-risk; and high-risk CSPs. Pentobarbital sodium injection compounding would be designated as a high-risk CSP because a non-sterile bulk powder API is incorporated into a finished, compounded preparation. It is then subjected to a terminal sterilization process, which is required under USP <797> for high risk compounded sterile products. This may be accomplished by any number of physical, chemical, or mechanical methods. In many compounding pharmacies, the preferred method of terminal sterilization is through use of membrane filtration.

In accordance with USP standards and definitions, a solution intended for parenteral administration is titled an "injection." A compounded pentobarbital sodium injection must contain the pentobarbital sodium API and one or more inactive ingredients to form the solution. One of these inactive ingredients must be a liquid vehicle to serve as a diluent to dissolve the solid powder API form. Water is the primary diluent used to prepare the commercial (manufactured) form of pentobarbital sodium injection, and it is highly probable that compounding pharmacies are using water in their pentobarbital sodium injection CSPs. In addition, compounding pharmacies may be including other inactive ingredients, e.g., propylene glycol, alcohol, hydrochloric acid, sodium hydroxide. Small amounts of these ingredients may be added, for example, to adjust pH, tonicity, and solubility of the finished preparation.

The manual combination or mixing of these ingredients, that is, the "compounding" process, must be carried out under specific environmental conditions, using equipment that is properly calibrated and maintained, and performed by personnel that are highly trained and whose competency and aseptic technique is verified at regular intervals. Sterile compounding of pentobarbital sodium injection must be done in a Direct Compounding Area that has ISO 5 quality airflow within a primary engineering control (e.g., a HEPA-filtered, horizontal laminar airflow workbench) that is located within a clean room that has ISO 7 quality airflow, as well as numerous additional design features. The airflow in the clean room and in the primary engineering controls must be certified at regular intervals by certified HVAC engineers. In addition, USP <797> has robust expectations for cleaning and maintenance of the clean room and compounding equipment, as well as quality assurance processes and quality control testing of the equipment for microbial and other non-viable particulate contaminants. Compliance with these USP <797> requirements is mandatory.

As can be inferred from the previous paragraph, pharmaceutical compounding of sterile products is a highly technical process that requires precision and has a very narrow tolerance for error. Pharmacies that choose to provide compounded sterile products must make substantial commitments for facilities, equipment, skilled personnel, training, quality programs (i.e., quality assurance, quality control, quality improvement), standard operating practices, and record

retention practices. Moreover, compounded sterile products such as pentobarbital sodium injection have additional risks in view of the utilization of nonsterile bulk API in the compounding process. While I do not have access to the exact process used by the compounding pharmacy in this case, my compounding knowledge and experience suggests the following steps, not necessarily in this order, nor limited to only these steps:

- Obtain pre-work materials, inventory and controlled substance record documentation, labeling, review master compounding and batch form records
- Collect container of bulk API (i.e., pentobarbital sodium powder) and other pharmaceutical ingredients to be used in compounding the preparation, as well as the accessories used to compound (e.g., syringes, needles, containers, disinfecting chemicals, etc.)
- Conduct hand hygiene and proper donning of sterile compounding garb (e.g., gloves, hair cover, mask, shoe covers, gown)
- Enter compounding clean room, preparing laminar airflow workbench, arrange materials in organized fashion
- Conduct compounding activities, weighing proper amount of bulk API, measuring proper volume of diluent and other inactive ingredients
- Using aseptic technique, add API and inactive ingredients into a container and observe powder to completely dissolve into solution
- Upon dissolution, use membrane filtration to terminally sterilize the finished preparation
- Check the integrity of the membrane filter to ensure it has remained intact
- If required, obtain samples for additional quality testing (e.g., sterility testing, bacterial endotoxin testing, potency testing, purity testing, pH testing, etc.

As previously stated, this is a general description of the process, and there could be several other steps depending on the operations of the pharmacy facility and number of preparations being compounded.

## C. BEYOND-USE DATING AND PRODUCT LIFE CYCLE

Traditional and Non-Traditional compounding pharmacies do not have access to the sophisticated equipment (e.g., spectroscopes, chromatographs, calorimeters, etc.) for qualitative and quantitative analysis that are typically found in pharmaceutical manufacturer establishments. This sophisticated equipment is important for measuring chemical, physical, and biological parameters to extend shelf-life of CSPs. Accordingly, Traditional and Non-Traditional compounders must limit their batch "production" sizes and settle for relatively short "beyond use dates" and thus limited commercial opportunities.

A "beyond use date" ("BUD") is defined in USP <797> as "the date or time after which a CSP shall not be stored or transported. The BUD is determined from the date and time the preparation is compounded." BUDs are typically assigned on the basis of professional experience and judgment and rarely based on batch-specific chemical analysis. Thus, a BUD is an empiric determination. Although BUD is sometimes used interchangeably with "expiration

date," these terms have different meaning. Expiration dates are assigned to manufactured products based on rigorous analytical and performance testing. The "expiration" date of FDA regulated pharmaceuticals is a qualified assurance that they retain their integrity over specified periods of time. This assurance is more difficult to do with compounded drugs. In the traditional compounding setting, it is also often unnecessary, as a particular drug is mixed pursuant to a licensed prescriber's order for an individual patient for immediate use.

Longer BUDs ("extended BUDs") can be established for CSPs using empirical data based on extended stability and sterility testing. This testing is conducted by a laboratory or, in the absence of such data, can be calculated according to the recommended ranges established under USP <797>. The calculation of an extended BUD is dependent on numerous variables, including, pivotally, the stability and sterility of the subject compounded drug:

> Pharmaceutical stability depends on the purity and concentration of specific ingredients, packaging and environmental exposure and storage . . . Small changes in any of those variables can cause rapid loss of drug strength or much shorter than expected shelf-life. . . . even the most expert and caring pharmacist's visual, olfactory or other professional judgment, in the absence of scientific testing results about sterility and stability of compounded pharmaceuticals can be dangerously wrong.

Newton, David and Dunn, Bernard, *A Primer on USP Chapter <797> "Pharmaceutical Compounding–Sterile Preparations," and USP Process for Drug and Practice Standards*, p.11.[9]

Even after it is assigned to a CSP, a BUD can be affected dramatically by subsequent storage conditions.[10] CSPs (such as pentobarbital sodium injection) need to be kept in very particular conditions, relating to the stability and properties of the medicines in question. If not stored properly, CSPs can be damaged and rendered unusable. The multiplicity of variables underscores the impossibility of reliable date certain BUDs and the importance of subsequent testing – and stability and sterility testing in particular – multiple times over a drug's shelf life, not just shortly after it is compounded. *Id.*; *see also* USP Chapter <795> "Stability Criteria and Beyond-Use Dating."

As set forward in USP <797>, these are the empiric BUDs for CSPs:

| **Risk Level** | **Room Temp** | **Refrig** | **Freeze** |
|---|---|---|---|
| Low | 48 hr | 14 days | 45 days |
| Low (12 hr BUD) | 12 hr | 12 hr | n/a |
| Medium | 30 hr | 9 days | 45 days |
| High | 24 hr | 3 days | 45 days |

[9] Available here: www.nhia.org/members/documents/usp_797_primer.pdf

[10] *See id.* at 40.

Thus, the maximum BUD (timed from the day and hour of preparation) that can be assigned to these products is:

- 24 hours, if CSPs are stored at controlled room temperature
- 3 days, if CSPs are stored at a cold temperature (i.e., refrigerated)
- 45 days, if CSPs are stored in a solid, frozen temperature.

While it is impossible to assess the accuracy of a BUD without knowing detailed information about the compound, the raw ingredients, the compounders, and the testers, it is possible to review the relevant science and codes to recognize the unreliability of a stated "expiration date" beyond an intended immediate use of the compounded drug.

I hope you find this information helpful and responsive to the Court's April 1, 2015 Order. If I can provide further clarification or explanation, please let me know. As you are aware, I was not asked to apply these standards or practices to the State of Texas's use of compounded pentobarbital for purposes of execution by lethal injection. As always, the application of scientific protocols to a specific set of facts or circumstances could affect my views and opinions because the protocols and/or tests that must be taken into account could compel a different discussion. Please let me know if I can be of further assistance as your litigation proceeds.

Sincerely,

James H. Ruble